PB80-213911

Pronamide
Position Document 2/3

(U.S.) Environmental Protection Agency
Arlington, VA

15 Jan 79

U.S. Department of Commerce
National Technical Information Service
NTIS

PB80-213911

Pronamide: Position Document 2/3

Special Pesticide Review Division
Office of Pesticide Programs
U.S Environmental Protection Agency

EPA/SPRD - 80/68

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U. S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

50272-101

REPORT DOCUMENTATION PAGE

1. REPORT NO. EPA/SPRD-80/68

2.

3. Recipient's Accession No. PB 80 213911

4. Title and Subtitle
Pronamide: Position Document 2/3

5. Report Date
1/15/79

6.

7. Author(s)

8. Performing Organization Rept. No.

9. Performing Organization Name and Address
Special Pesticide Review Division
Environmental Protection Agency
CM#2
Arlington, VA

10. Project/Task/Work Unit No.

11. Contract(C) or Grant(G) No.
(C)
(G)

12. Sponsoring Organization Name and Address
Environmental Protection Agency
401 M St. S.W.
Washington, D.C. 20460

13. Type of Report & Period Covered

14.

15. Supplementary Notes

16. Abstract (Limit: 200 words)

Risk/benefit analysis: qualitative & quantitative risks of a pesticide, value of crop uses, availability of alternative pesticides, exposure to man and environment. Identification of risk reducing regulatory options and proposed Agency action.

17. Document Analysis a. Descriptors
0606

b. Identifiers/Open-Ended Terms
0504

c. COSATI Field/Group

18. Availability Statement:
Release Unlimited

19. Security Class (This Report)
Unclassified

20. Security Class (This Page)
Unclassified

21. No. of Pages

22. Price

(See ANSI-Z39.18) See Instructions on Reverse OPTIONAL FORM 272 (4-77)
(Formerly NTIS-35)
Department of Commerce

PRONAMIDE TECHNICAL SUPPORT TEAM

Richard Troast, Project Manager, SPRD, OPP

George Beusch, Section Head, HED, RCB

Harry Day, Chemist, HED, EFB

Roger Gardner, Pharmacologist, HED, TOX

Kevin Keaney, Senior Regulatory Policy Analyst, SPRD, OPP

George Keitt, Ph.D., Plant Physiologist, BFSD, PSB

John Leitzke, Ecologist, HED, EEB

Dorothy Patton, Attorney, OGC

Linda Zygadlo, Economist, BFSD, EAB

Table of Contents

Page

I. Introduction..1

A. Background..1

B. Registered Uses and Production........................2

C. Regulatory History 2

1. Tolerances..2

2. Pre-RPAR Actions...................................3

3. Post-RPAR Actions..................................3

II. Analysis and Assessment of Risk.......................5

A. Basis of Presumption.................................5

B. Rebuttal Arguments...................................5

1. Lack of Sufficient Exposure.........................5

2. The Carcinogenesis of Pronamide.....................6

3. Lack of Carcinogen Risk Assessment in the RPAR Notice....................................7

4. The Mouse in Not an Acceptable Model for Carcinogenic Tests...............................7

5. Tumors Caused by Pronamide are Not De Novo........8

6. Negative Mutagenicity Tests Indicate a Non-Carcinogen...................................9

C. Exposure Analysis.................................. 9

1. Dietary Exposure...................................10

2. Applicator Exposure................................10

D. Risk Assessment......................................17

a. Discussion of Proposed Restrictions..........61

(i) Classify Pronamide as a Restricted Use Pesticide and Require Applicator Certification..........61

(ii) Require the Use of Protective Clothing During Mixing and Application of Pronamide..........62

(iii) Require the Formulation of Pronamide (Wettable Powder) in Water Soluble Bags...63

(iv) Cancel Hand Spray Use..........64

3. Continue Registrtaion of All Uses, Amend the Terms and Conditions of Registration; Revise the Tolerance on Lettuce to Lower the Dietary Exposure..........65

4. Continue Registration of All Uses; Amend the Terms and Conditions of Registratin; Revise the Tolerance on Lettuce to Lower the Dietary Exposure; Require a Monitoring Report on Residues in Milk from Pronamide Use in Alfalfa at 5 Year Intervals Coincident with Reregistration..68

5. Cancel All Uses..........69

C. Comparison of Options..........71

V. Recommended Regulatory Action..........73

A. Recommendation of Options 4..........75

Bibliography..........81

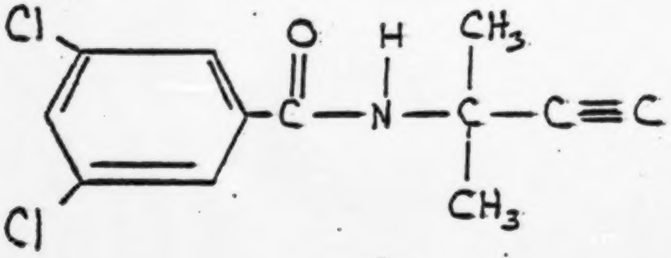
Appendices..........85

I. Introduction

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the related regulations requires the Environmental Protection Agency (EPA) to review the risks and benefits of the uses of the pesticides which it registers. The determination that pronamide poses a risk of oncogenicity (based on tumors found in test animals) caused the Agency on May 20, 1977, to issue a notice of rebuttable presumption against the registration and continued registration (RPAR) of pesticide products containing pronamide. The Agency's analysis of the risks and the benefits of the continued use of pronamide and the Agency's recommendations for regulatory alternatives are presented in this Decision Document.

A. Background

Pronamide is a substituted benzamide which is known by the trade name KERB. Pronamide is synthesized as a solid. The technical chemical is packaged as a coarse powder formulation. Pronamide products that are ready for application are wettable powders or granulars. The structural formula for pronamide is given below:



B. Registered Uses and Production

Rohm and Haas, the only registered producer of technical grade pronamide, is also the largest formulator of pronamide products (Kerb 50W). Pronamide is used primarily as an herbicide in lettuce and alfalfa. Pronamide is also used for other purposes (i.e., controlling weed and grass in ornamental turf and commercial nursery planting, Table III-1). However, the amount of pronamide used for other purposes is significantly less than the amount used in lettuce and alfalfa. Rohm and Haas exports pronamide to Canada, South Africa, Spain, Italy, the United Kingdom, France, and Japan.

C. Regulatory History

1. Tolerances

The tolerances set for pronamide in raw agricultural commodites are listed below. These tolerances were established on the basis of studies presented to the Agency from 1969 to 1975 (40 CFR 180.317).

Alfalfa	10 ppm
Clover and Forage Legumes	5 ppm
Lettuce and Endive (Escarole)	2 ppm
Blueberries and Cane Fruit (Blackberries Boysenberries and Raspberries)	0.05 ppm
Kidney and Liver of beef cattle goats, hogs, poultry, horses and sheep	0.2 ppm
Eggs, meat, milk, fat and meat by-products except (kidney and liver) of cattle, goats, hogs, horses, poultry, and sheep.	0.02 ppm

2. Pre-RPAR Actions

Data from two chronic feeding studies are required by the Agency as part of the pesticide registration requirements for tolerance setting. Rohm and Haas submitted data in 1971 for rats (Pesticide Petition 1F1139) and in 1974 for mice (Pesticide Petition 5F1552). The rat study did not indicate the formation of tumors at the dosages tested. The data presented in the mouse study indicated that, at dietary concentrations of 1,000 and 2,000 ppm, pronamide caused hepatocarcinomas in male mice (Coberly, 1974). The Criteria and Evaluation Division (CED) (Potrepka, 1977) in the Office of Pesticide Programs (OPP) and the Agency's Carcinogen Assessment Group (CAG) (Albert, 1977) reviewed these data, confirmed the conclusions from the preliminary review of the mouse data, and concluded that pronamide is a carcinogen in male mice. The Agency based the RPAR against pesticide products containing pronamide on this data and related reviews.

3. Post-RPAR Actions

Two registrants (Swisher, 1977; Clark, 1977) requested a 60-day extension of the rebuttal period asserting that the regular 45-day period was not sufficient to prepare a rebuttal document on all the data in the RPAR notice. The Agency granted an extension to August 27, 1977, for the filing of rebuttal data by all registrants and other interested parties.

During the response period, registrants and other interested parties had an opportunity to review the data upon which the presumption was based and to submit rebuttal information. Respondents could rebut the presumption by showing that the Agency's initial determination of risk was in error, or that pronamide "will not concentrate, persist or accrue to levels in man or the environment likely to result in any significant chronic adverse effects" [40 CFR 162.11(a)(4)]. Also, registrants and other interested persons were offered the opportunity to submit evidence as to whether the social, economic, and environmental benefits of the use of the pesticide outweigh the risk of its use [162.11(a)(5)(iii)].

This Position Document details the Agency's review of the risks, benefits and regulatory options which relate to the uses of pronamide. Section II presents the Agency's conclusion that the information submitted by respondents has not rebutted the presumption against registration, as well as its assessment of the risks associated with the use of pronamide. Section III contains the Agency's analysis of the benefits of pronamide as well as the probable costs of regulatory action to cancel or to otherwise restrict the uses of this pesticide. A comparison of the environmental impacts of the proposed regulatory options, weighing both risks and benefits, is presented in Section IV, while Section V presents and explains the Agency's recommended option.

II. Analysis and Assessment of Risk

A. Basis of Presumption

The Agency's presumption against the registration of pronamide was based upon an 18 month mouse chronic feeding study conducted by Rohm and Haas which indicated a significant increase ($p<0.05$) in hepatocellular carcinomas at the 1,000 and 2,000 ppm levels (PP 5F1552). There was an observed, statistically significant dose-response relationship.

B. Rebuttal Arguments

There were 123 rebuttals received. Only two of these dealt with substantive rebuttal issues and are addressed in the following section. The remainder of the rebuttals addressed themselves to the benefits of the continued use of pronamide. These comments are addressed in Section III, the Benefits Analysis.

1. Lack of Sufficient Exposure

One respondent argued that human exposure to pronamide or its residues is not sufficient to warrant concern. The respondent argued that the low exposure involved would be below the no observable effect level (NOEL) for oncogenic effects, and therefore no increased incidence of tumors would be observed (Rarig, 1977).

This argument fails for two reasons. First, tumors were reported at both of the dose levels tested in the Rohm and Haas study. Therefore, a NOEL was not demonstrated in the mouse study cited in the RPAR, nor in any of the data submitted in response to the RPAR, and there is no basis for arguments based on a NOEL for pronamide.

Second, no demonstrated NOEL, has been provided and in that case the Agency's carcinogen policy (41 FR21402, May 25, 1976), assess risk on the basis of no-threshold in which case even low lwvels of exposure are viewed as a potential cancer risk. Residues of pronamide do exist in foods. Market basket surveys have found residues of pronamide in the lettuce sold to consumers (Rarig, 1977). A recently completed residue analysis of California head lettuce has demonstrated pronamide residues of up to 0.09 ppm (Alford, 1978). In light of the Agency's no-threshold policy and the absences on any NOEL data coupled with positive, this documentation of the presence of pronamide residue in lettuce also refutes the respondent's argument.

2. The Carcinogenesis of Pronamide

Two respondents have stated that toxicologists disagree on whether or not pronamide is actually a carcinogen (Rarig, 1977; USDA, 1977). The results of the "Eighteen-Month Study on the Carcinogen Potential of Kerb (RH-315; Pronamide) in Mice" provide substantial evidence, according to the terms of the Agency guidelines, that pronamide is oncogenic, i.e., tumors were observed and reported at two feeding levels (1,000 and 2,000 ppm), in the male mouse. In assessing the rebuttal, the Carcinogen Assessment Group (CAG) examined the original histopathology slides in the mouse study. The consultant pathologist performing the review for the CAG (Dubin, 1978) concurred with the original review of the slides by Rohm and Haas. The CAG thus confirmed the original observation of Rohm and Haas that pronamide causes an increased incidence of tumors in mice. Further, although toxicologists may have originally disagreed on the magnitude of the carcinogenic potential, different interpretations do not, per se, invalidate an affirmative interpretation, and the pathologists in general did agree that pronamide is an ocogenic agent.

3. Lack of Carcinogen Risk Assessment in the RPAR Notice

One commenter claimed that EPA is required to perform a carcinogenic risk assessment before issuing the RPAR (Rarig, 1977).

The Interim Cancer Guidelines (41 FR 21402, May 25, 1976) clearly state that the assessment of carcinogenic risks is prepared after the Rebuttable Presumption Against Registration is issued.

4. The Mouse is Not An Acceptable Model for Carcinogenic Tests

One commenter claimed that the mouse is not an appropriate test model since the mouse is prone to tumors which have no bearing on human carcinogenesis (Rarig, 1977).

The Interim Cancer Guidelines state that animal data is regarded as "substantial evidence" in judging the total weight of evidence of whether a substance is carcinogenic (41 FR 21402, May 25, 1976).

5. Tumors Caused by Pronamide Are Not De Novo

One respondent attempted to rebut the presumption by arguing that pronamide-induced tumors do not arise *de novo*, but arise secondarily to stresses placed on the hepatic tissue (Rarig, 1977).

The CAG (Albert, 1978) evaluated this argument and found it to be ambiguous, because it was not made clear whether the argument was referring to focal hyperplasia or to generalized hyperplasia. The CAG therefore addressed both conditions. If the rebuttal statement was referring to focal hyperplasia in arguing that tumors caused by pronamide do not arise *de novo*, the CAG stated that this argument is illogical since experimental evidence indicates that hypertrophy and hyperplasia are recognized characteristics in the neoplastic progression of liver tumors. If the rebuttal comment was referring to generalized hyperplasia, and was arguing that it was this condition which pronamide caused and that the malignancy developed secondarily to the hyperplasia, the CAG stated that this argument is also illogical because generalized hyperplasia and hypertrophy are not characteristi responses to pronamide. Thus, even if such responses occurred, there is no further substantiating evidence which would assign to pronamide the role of a promoting agent with a threshold type of dose-response pattern.

6. Negative Mutagenicity Tests Indicate a Non-Carcinogen

One respondent attempted to rebut the presumption by arguing that because pronamide does not produce mutations in the host-mediated assay (Ames Assay)(Rarig, 1977) and because of the close correlation between mutagenicity and carcinogenicity, pronamide is not a true carcinogen.

The CAG replied (Albert, 1978) that a negative mutagenic assay does not necessarily indicate that a chemical is also not a carcinogen because there are other plausible mechanisms of carcinogenesis (e.g., altered gene regulation). Further, while a strong correlation exists between positive results in mutation assays and in vivo mammalian bioassays, not all known carcinogens induce mutations in the Ames test. More specifically it is known that other chlorinated aromatic hydrocarbons, the chemical class of which pronamide is a member, have previously given false negative results in the Ames test.

C. Exposure Analysis

Rohm and Haas Company and the U.S. Department of Agriculture provided data on patterns of pronamide use which the Agency has used both to identify the populations exposed to pronamide and to estimate the extent of the populations' exposure. An average person was assumed to weigh 60 kg and to consume 1.9 kg of food daily.

1. Dietary Exposure

The Agency's estimates of human dietary exposure are based on tolerance data, residue data, and data indicating the extent to which pronamide is used on each of the food crops for which it is registered (Day and Collier 1978). A reasonable upper limit of the U.S. population's exposure to pronamide in the diet was calculated, based on the average person's dietary intake. If residue data for commodities treated with pronamide were unavailable, tolerance data were used. The resulting dietary exposure values are presented in Table II-1. The annual dietary exposure from the ingestion of foods treated with pronamide is estimated to be 10.95 mg/person.

It should be noted that Table II-1 assumes an equal distribution of pronamide treated food across the U.S. and an average consumption of this food by individuals. In fact, however, it is likely that some will be exposed less to pronamide, depending upon the availability of treated food in their geographic area and on their eating habits.

2. Applicator Exposure

There are three types of personnel involved in the application of pronamide: custom applicators (lettuce), grower applicators (alfalfa), other applicators (homeowners, commercial nursery personnel, and berry growers). The number of custom applicators exposed to pronamide is estimated at 20 persons. This segment of the occupationally exposed population has the highest calculated exposure, since custom

TABLE II-1. Pronamide Levels in the Diet

Product	Tolerance (mg/kg)	Consumption kg/person/day	Total mg/person/day Pronamide intake if all food Contained Maximum Tolerance Dose of Pronamide	Corrected mg/Person/ Day Pronamide Intake Based on % of Total U.S. Crops Treated (See Notes Below)
Lettuce	2.0	0.026	.05	0.03 (.0008 – .01)[1/]
Berries	0.05	0.0006	.00003	—
Eggs	0.02	0.055	.001	.0001
Meat	0.02	0.274	0.005	.0001
Milk and Dairy Products	0.02	0.567	0.011	.0001
Total			0.06703	0.03 (0.0012–.01)

1/ Figures in parentheses reflect actual residue data.

The following facts formed a basis for the dietary levels of corrected mg/person/day pronamide intake:

a. The proportion of lettuce treated with pronamide in the minor producing states totals 50-55% of the production (Keitt, 1978).

b. Based on information from the registrant at a minimum label recommended treatment to harvest interval of 35 days a residue of 0.8ppm can be expected. An average lettuce season is 90 days (Rarig, 1977). Surveillance data on commercially harvested lettuce having a treatment to harvest interval from 77-107 days (92 day mean) ranged from 0.01 to 0.138ppm with a mean value of 0.05 for six samples of six replicates each. Residue studies from California show mean residues of <0.05 with treatment to harvest intervals of 63 days minimum (Alford, 1978). Residue studies from New Jersey grown lettuce gave residues ranging from <0.01 to .15 ppm with a minimum treatment to harvest interval of 60 days (Rarig, 1977). Therefore actual residue values from lettuce collected in the market place can reasonably be expected to have residue levels ranging from 0.05 to 0.8ppm instead of the 2.0ppm tolerance. The tolerance values are used in other residue calculations since this is the legally allowable upper limit.

With the facts as stated in a. and b. the following assumptions were then made to arrive at the corrected mg/person/day pronamide intake.

a. Food containing pronamide residues is equally distributed throughout U.S. population before consumption.

b. Pronamide residues in milk will be equally distributed in all dairy products whether processed or not.

c. Alfalfa consumed by meat and dairy cows throughout U.S.A. all contains a weighted average amount of pronamide.

d. Out of a total of 75.4 $X10^6$ tons of alfalfa grown in U.S., 0.42 $X 10^6$ tons (0.55%) is treated with pronamide.

application is the prevalent method of using pronamide in lettuce fields and more than 40% of the pronamide used is used on this crop. The individual grower of alfalfa is normally the applicator, so his exposure is similar to that of the custom applicator. The number of grower applicators is estimated to be 3800. The alfalfa grower uses pronamide only once a year, unlike the custom applicator who uses it several times yearly. Therefore, the total yearly exposure of individual grower applicators to pronamide in alfalfa operations would be less than the total yearly exposure of individual custom applicators in lettuce operations. Applicators who use pronamide for other purposes use it only once a year and use the wettable powder formulation or a pronamide/fertilizer product (turf applicators only). The exposure of these applicators should not exceed the exposure which alfalfa growers receive, and may be less depending on the formulation they use and the size of the area on which they use it.

The annual unit exposure to applicators from pronamide is based on three studies. One of the studies used to estimate exposure was the model of Wolfe (H.R. Wolfe, 1967 and H.R. Wolfe, 1975). The Wolfe model considers exposure resulting from bag opening, mixing, and applying a chemical (parathion). The two other studies (Krezmenski, 1978; Jegier, 1964) consider exposure resulting from bag opening and mixing using pronamide. The values calculated from these models are reflected in Table II-2 (lettuce) and Table II-3 (alfalfa).

Table II-2. Cumulative Occupational Exposure to Custom Applicators - Lettuce

	Santa Maria Valley	Salinas Valley	Imperial Valley	Other Areas in California	Arizona
Total Acres	13,200	60,280	26,500	14,550	9,250
Total Applicators (estimate)	1.75	8	3.5	1.9	1.2
Total ai applied per acre	0.9	0.5	1.1.	0.5	1.1
Bag openings per applicator	4,525	2512	5,552	2,552	5,652
Annual dermal exposure (from bag openings) per applicator per kg body wt per year	W**4,525 J*** 996 RH****317	2512 552 176	5552 1221 389	2552 561 179	5652 1243 395
Annual dermal exposure (during spray treatment) per applicator per kg body wt per year*	W 5 RH 0.5	5 0.5	5 0.5	5 0.5	5 0.5
Annual inhalation exposure (from bag openings) per appplicator per kg body wt per year	W 9.0 J 22.6 RH 1.8	5.0 12.5 1.0	11.0 27.5 2.2	5.0 12.5 1.0	11.0 27.5 2.2
Total Exposure from Bag Opening	W 4534.0 J 1018.6 RH 318.8	2517.0 564.5 177.0	5563.0 1248.5 391.2	2557.0 573.5 180.0	5663.0 1270.5 397.2
Annual inhalation exposure (during spray treatment) per applicator per kg body wt per year*	W .03 RH .01	.03 .01	.03 .01	.03 .01	.03 .01
Totals Exposure from Application	W 5.03 RH 0.51	5.03 0.51	5.03 0.51	5.03 0.51	5.03 0.51

*Based on 50 treatment days per year.

**Wolfe

***Jegler (no applicator exposure studies were conducted by Jegler)

****Rohm and Haas

Table II-3. Cumulative Occupational Exposure to growers - Alfalfa

Total Acres		94,500	
Average Acres of Alfalfa Hay Grown Per Farm		49	
Total Number of Farms Using Pronamide		1928	
Total Bag Openings per year		49	
Total Number of Applicators		3856	
Annual Dermal Exposure from Bag Openings	W*	49.0	mg/kg body weight
	J**	10.8	mg/kg body weight
	RH***	3.4	mg/kg body weight
Annual Inhalation Exposure from Bag Openings	W	0.1	mg/kg body weight
	J	0.25	mg/kg body weight
	RH	0.02	mg/kg body weight
Total Loader Exposure	W	49.1	mg/kg body weight
	J	11.1	mg/kg body weight
	RH	3.4	mg/kg body weight
Annual Dermal Exposure from Application	W	0.1	mg/kg body weight
	RH	0.01	mg/kg body weight
Annual Inhalation Exposure from Application	W	0.0005	mg/kg body weight
	RH	0.0001	mg/kg body weight
Total Applicator	W	0.1	
	RH	0.01	
Total		49.2 - 3.40mg/kg body weight	

*Wolfe
**Jegier
***Rohm and Haas

Each of the studies used in determining exposure is not directly applicable to the field use of pronamide or is flawed. For example the Wolfe study used a 1% product while the actual use of pronamide involves using a 50% product. An extrapolation from a model using a 1% TEPP product to draw conclusions regarding a 50% product may introduce a substantial overestimation. These overestimations would occur since such an extrapolation assumes a linear relationship which may not exist. The Rohm and Haas study is weak since only one replicate was made of the work and since it underestimated exposure by measuring glove area instead of hand area. Therefore, while the complete applicability of all of the studies is weak to some extent, the Agency considers the Jegier work to represent a reasonable average exposure value. For the purposes of this analysis the values based on Wolfe will be taken as the upper limits of exposure and those from the Rohm and Haas study will be taken as the lower limits of exposure. The range of values calculated from these models reveal potential yearly exposure for custom applicators (lettuce) and range from 4,159 mg/kg using Wolfe's model, to 915 mg/kg using Jegier's model, to 291 mg/kg using the Rohm and Haas data. For alfalfa growers, the potential yearly exposure is 49 mg/kg using Wolfe, 11.2 mg/kg using Jeiger, and 3.4 mg/kg using Rohm and Haas' data. These values are due to dietary and occupational exposure to pronamide. The oral exposure (0.18 mg/kg) is an insignificant addition to these values.

The exposure to pronamide of homeowner/turf maintenance specialists through a pronamide fertilizer product is 50 times less than the comparable exposure of alfalfa growers. In addition, a pronamide/fertilizer compound would be a granular product, not a wettable powder, thus minimizing inhalation exposure. Dermal exposure would be similarly minimized by the granular formulation (Day and Collier, 1978). Consequently, any exposure to this segment of the population is smaller than the exposure to alfalfa applicators.

The exposure from hand spraying, which could be common in certain uses (berries and nursery stock), is more difficult to estimate because the clothing, equipment, time exposed, application rate, and other factors are undetermined variables. However, again using the data developed from Wolfe (Wolfe, 1967), a calculated estimate of the total exposure from this type of application is 0.9 mg/kg/hr. Assuming that growers would switch to mechanical spraying in order to cover larger areas, their total exposure should not exceed that calculated for alfalfa growers. Thus, applicators who use pronamide for other purposes would receive a maximum annual exposure to pronamide of 49 mg/kg, 11.2 mg/kg, or 3.4 mg/kg (depending on the model used to calculate the exposure).

D. Risk Assessment

The cancer risk assessment for pronamide is based on the principles and procedures outlined in the EPA Interim Cancer Guidelines (41 FR 21402, May 25, 1976). These guidelines specify that a substance will be considered a "presumptive cancer risk when it causes a statistically significant excess incidence of benign or malignant tumors in humans or animals", that current and anticipated exposure levels are appropriate considerations, and that cancer risk estimates may be derived from a variety of risk extrapolation models.

The CAG reviewed the oncogenicity data, concluded that pronamide did produce statistically significant numbers of hepatocellular tumors in male mice (Albert, 1977), and used this data in the one-hit model to estimate the cancer risk (Albert, 1978). The one-hit slope parameter estimate based on each exposure level separately is derived from the following equation:

$$B = \ln [(1 - P_o) - (1 - P_x)] / D$$ [1]

for the mouse data, substituting the appropriate responses gives:

$$B = \ln [(1 - 7/96) - (1 - 21/96)] / 1000 = 1.711 \times 10^{-4}$$ [1]

for the low dose and

---

[1] B = slope.
ln = natural logarithim.
Po = mice with liver tumors in control.
Px = mice with liver tumors in low dose (1,000ppm).
mice with liver tumors in high dose (2,000ppm).

$$B = \ln [(1 - 7/96) - (1 - 35/98)]/2000 = 1.831 \times 10^{-4}$$

for the high dose. These estimates were well within the normal biological variability of each other and thus provide support for the choice of the linear one-hit model.

The CAG estimate, that the lifetime probablity of a cancer due to ingestion of pronamide is provided by the following equation:

$$P = (1.711 \times 10^{-4})X,$$

where X is the ppm in the diet. Table II-4 gives the individual risks associated with ingestion of pronamide by commodity. The sum of the risks from dietary exposure will range from 3.01×10^{-6}, assuming residues in lettuce of 2.0 ppm, to 1.01×10^{-7}, when residues in lettuce are 0.05 ppm.

For applicator exposure the CAG estimates an equivalent dietary exposure. An example calculation of dietary equivalence is illustrated below for exposure due to bag openings.

$$\frac{60 \times 3692 \times 40}{365 \times 70 \times 1.94} = \frac{\text{lifetime dose mg}}{\text{lifetime food intake}} = 178.7 \text{ ppm } ^{1/}$$

1/
60 = 60 kg. person
3692 = annual bag openings at 1 mg/kg exposure
40 = 40 yr. working history
365 = days/year
70 = years average lifespan
1.94 = daily food intake (kg)

Table II-4
Risk and Expected Cancers Associated with the Ingestion of Pronamide

Product	Corrected mg/Person/ Day*	Lifetime Average ppm in diet	Lifetime Probability of Cancer Due to Ingesting Pronamide	Expected Numb Cancers per Year
Lettuce	.0008	4.29×10^{-4}	7.42×10^{-8}	0.23
	.01	6.86×10^{-3}	1.18×10^{-6}	3.66
	.03	1.72×10^{-2}	2.98×10^{-6}	9.24
Eggs	.0001	5.20×10^{-5}	8.90×10^{-9}	0.03
Meat	.0001	5.20×10^{-5}	8.90×10^{-9}	0.03
Milk	.0001	5.20×10^{-5}	8.90×10^{-9}	0.03
Berries*	Not Significant..............................			
Total When Residue in Lettuce is				
	.05 ppm		1.01×10^{-7}	0.32
	.8 ppm		1.21×10^{-6}	3.75
	2.0 ppm		3.01×10^{-6}	9.33

Exposure estimates from all the studies (Wolfe, Jegier, and Rohm and Haas) were inserted into the dietary equivalence equation and an exposure value concentration in ppm was determined. This exposure value was then inserted into the equation to obtain the risk assessment. The assessment of the risk for applicators, Table II-5, reports a risk calculation only for the mixing operation based on the exposure estimates from each of the three models. This calculation is the highest calculated exposure value and consequently represents the highest risk. All other risk calculations are based on exposure calculations which use Wolfe's model, since the exposure for application operations is less by several orders of magnitude than that for the mixing operation.

Table II-5
Risk and Cancer Potential Associated with the Application of Pronamide to Alfalfa and Lettuce

Source of Exposure	Route of Exposure	Exposure Levels mg/kg/yr			Exposure Levels Lifetime average ppm			Lifetime Possibility of Cancer Due to Pronamide			Expected Cancers Per Year
Alfalfa 1/		W*	J**	RH***	W*	J**	RH***	W*	J**	RH***	
Bag Opening During Mixing Operations	Dermal Inhalation	49.0 0.1	10.8 0.25	3.4 0.02	2.37 4.84×10^{-3}	0.52 0.01	0.16 0.0009	4.06×10^{-4} 8.28×10^{-7}	8.89×10^{-5} 1.7×10^{-6}	2.73×10^{-5} 1.54×10^{-7}	
Spraying Operations	Dermal Inhalation	0.1 0.0005	—	—	4.84×10^{-3} 2.42×10^{-5}	—	—	8.28×10^{-7} 4.14×10^{-9}			
Total		49.2	11.5	3 4	2.38	0.5	0.16	4.06×10^{-4}	8.93×10^{-5}	2.84×10^{-5}	
Lettuce								W*	J**	RH***	
Bag Opening During Mixing Operations	Deraml Inhalation	3692 2	812 1.85	258 1.5	178.7 .1	39.3 2×10^{-4}	12.5 1×10^{-4}	3.06×10^{-2} 1.71×10^{-5}	6.73×10^{-3} 3.42×10^{-7}	2.14×10^{-3} 6.84×10^{-6}	
Spraying Operations	Dermal Inhalation	0.1 0.0005	—	—	4.84×10^{-3} 2.42×10^{-5}	—	—	8.28×10^{-7} 4.14×10^{-9}			
Total		3694	813.8	259.5	178.8	39.3	12.5	3.06×10^{-2}	6.73×10^{-3}	2.14×10^{-3}	
Total Applicator Risk + Dietary Risk 2/											
Alfalfa								4.09×10^{-4}	9.23×10^{-5}	3.14×10^{-5}	0.022
Lettuce								3.06×10^{-2}	6.73×10^{-3}	2.14×10^{-3}	0.007

1/ The applicator exposure levels for the minor volume uses should not excede applicator exposure levels for alfalfa, therefore the lifetime possibility of cancer from these minor volume uses should be comparable to the lifetime possibility of cancer for alfalfa.

III. Benefits Analysis

A. Introduction

This section of the position document was derived from the Preliminary Benefit Analysis of Pronamide which was prepared by the Benefits and Field Studies Division of EPA. Although only the major uses of Pronamide on lettuce and alfalfa are discussed in this section, the underlying report covered all of the uses reported in Table III-1.

The preliminary analysis presents information on the amount of the pesticide used, evaluations of its efficacy for weed control, articulations of pest-control strategies with and without pronamide, and on the identification of the economic impacts attending each strategy. Data for the Preliminary Benefit Analysis of Pronamide was developed in part using information supplied by Rohm and Haas, U.S. Department of Agriculture (USDA), and other interested parties.

B. Lettuce

1. Biology of Weed Control

Pronamide is applied annually to 123,900 acres of lettuce in California and Arizona as a basic component of a weed-control strategy which includes the use of both chemical and non-chemical techniques. Pronamide may be applied alone or in combination with other chemicals such as benefin. In either event, the use of herbicides is always supplemented with hand and mechanical cultivations.

Table III-1
Pronamide Use Patterns[1]

Site	U.S. Acres Grown	Acres Treated with Pronamide	% Acres Treated with Pronamide	Application Rate per Treated Acre	Aplications Per Year
Alfalfa Hay[2]	27,000,000	94,000	0.35%	1.0 lb/A	1
Alfalfa Seed	380,000	21,000	5.5%	1.25 lb/A	1
Clover Seed	370,000	8,000	2.2%	1.25 lb/A	1
Lettuce[3]	193,000	123,000	55.0%	1.0 - 2.0 lbA	1-3[4]
Woody Ornamentals	226,400	17,000	5.5%	1.5 lb/A	1
Turf	[5]	16,600	——	0.75 lb/A	1
Sugarbeet Seed	>3900[6]	>3900	——	1.0 lb/A	1
Berry Crops	9720	5250	54.0%	1.5 lb/A	1

1. EPA Benefits Assessment Report
2. Includes other legumes for forage
3. Lettuce assessment is California and Arizona only. These 2 states account for 87% of the U.S. lettuce production
4. There may be 3 lettuce crops per year on the same acreage with pronamide applied once per crop season
5. Total bermuda grass turf acreage not available
6. Total Sugarbeet seed acreage not available

The weed-control strategies currently used by lettuce growers in Arizona and California vary by region and season due to such factors as weed spectra (with both seasonal and geographical variation), soil types, crop rotations, temperature, and rainfall. Five lettuce producing regions --- Imperial/Blythe, Salinas, Santa Maria, other California areas, and Arizona --- use weed-control strategies which include the application of pronamide. Table III-2 reports the use of pronamide and benefin, the most widely used herbicides on lettuce in California and Arizona, in 1977. Pronamide is used to treat approximately 55 percent of the acreage on which lettuce is produced in these states. In the coastal growing areas of California, Salinas, Santa Maria, and Oxnard, 95 to 100 per cent of the acreage is treated with pronamide alone or in sequential treatments with either benefin, propham, or CDEC. In Arizona, pronamide, benefin, bensulide, and/or propham are used in combination with hand and mechanical cultivations to control weeds in lettuce. It is estimated that most of the winter-planted, spring-harvested lettuce in Arizona is treated with pronamide.

Pronamide is used as a basic component of weed-control strategies in lettuce due to its range of weed control. Pronamide controls a relatively broad spectrum of weeds, some of which no other registered herbicides will

Table III-2
Estimated Herbicidal Uses in California and Arizona Lettuce Acreage,[1] 1977

	CALIFORNIA					
Herbicides	Salinas Valley [a]	Santa Maria Valley [b]	Imperial Blythe [c]	Other[a] California	Arizona [d]	Total
			acres			
Pronamide	60,280	13,200	26,500	14,550[2]	9,250	105,780
Pronamide/ Benefin	18,120	Not Used	Not Used	Not Available	Not Available	18,120
Benefin & Other Benefin Combinations	Not Used	Not Used	26,500	Not Available	Not Available	Not Availa
Estimated Lettuce Acreage	60,400	13,200	53,000	29,100	38,050	193,750

control, specifically, those in the mustard family (shephard's purse, wild mustard, and London rocket). Table III-3 reports the control spectra achieved by pronamide and its alternatives as well as their relative ranking in efficacy. The methods of applying pronamide can vary. Growers can either apply it to the surface of the soil after they plant the lettuce seed (but before the emergence of weeds) and incorporate it into the soil by irrigating with sprinklers (the most common practice), or they can incorporate it into the soil before planting the lettuce seed and activate it by irrigating. Pronamide's methods of application allow use by lettuce growers in areas where, during the rainy months of the winter planting season, they cannot use chemicals which require incorporation into the soil. If growers till the heavy-textured soil of these areas when it is wet, the soil forms a hardpan several inches beneath the surface which the lettuce roots cannot readily penetrate.

Another advantage of the use of pronamide is that it has a short residual life which allows growers to grow most of the crops that are normally rotated with lettuce immediately after harvest. Residues of benefin (an alternative to pronamide which is currently used in some areas and which growers would be likely to include in any strategy of chemical weed-control to replace pronamide) are more persistent. The use of benefin would limit the crops that growers could plant following lettuce in rotation in all of the lettuce-growing areas.

Table III-3
Comparative Efficacy of Alternative Herbicides in Lettuce

Weeds		Herbicides					
		Pronamide	Benefin	Propham	Bensulide	CDEC	Benefin & Propham
Barnyardgrass		P	C	N	C	C	C
Burning nettle		C	P	C	N	C	C
Canary grass		C	P	C	C	N	C
Common groundsel		N	N	N	N	N	N
Crabgrass		C	C	N	C	C	C
Cupgrass		P	C	N	C	C	C
Fiddleneck		C	C	N	P	P	C
Goosefoot		C	C	N	P	P	C
Groundcherry		P	N	N	N	N	N
Hairy nightshade		C	N	C	N	N	C
Henbit		P	N	C	N	N	C
Knotweed		P	C	P	N	P	C
Lambsquarters		C	C	N	P	P	C
London rocket		C	N	N	N	N	N
Malva		C	N	N	N	P	N
Mustard		C	N	N	N	N	N
Pigweed		P	C	N	C	C	C
Prickly lettuce		N	N	N	N	P	N
Purslane		C	C	N	C	C	C
Shepherdspurse		C	N	N	N	N	P
Annual yellow sweetclover		P	N	N	N	N	N
Sowthistle		N	N	N	N	P	N
Volunteer cereals (barley, wheat, etc.)		C	N	C	N	N	C
Total	C	13	9	5	6	6	14
	P	7	2	1	7	7	1
	N	3	12	17	10	10	8

1/ C-Control; P-Partial Control; N-No Control

Source: University of California, Davis; Division of Agricultural Sciences, 1977

A substantial economic benefit from pronamide use depends on the weather conditions in several of the lettuce-growing regions. During optimal weather conditions, the alternative weed-control strategies are sufficiently efficacious to maintain yields at a level equal to those achieved through the use of pronamide. However, in the Salinas and Santa Maria Valleys, winter rainfall can delay the optimal timing of the mechanical and hand cultivation which is required in the absence of pronamide. The delay in cultivation could increase weed competition and ultimately reduce lettuce yields. No information was available to define optimal, normal, or adverse weather conditions as they affect use of herbicides in lettuce production. For example, the information generated in the analysis which supports this document does not enable an articulation of the number of days of rainfall which would be considered either optimal or adverse and, therefore, no estimate can be made of the frequency or intensity of the adverse impacts on yield. The only information which was available in this regard were the opinions of knowledgeable individuals in California who estimated that a prohibition of the use of pronamide on lettuce would result in a 20 percent decline in yield on 25 percent of the acreage (18,400) in the Salinas and Santa Maria Valleys. Their opinions were that this loss would occur under normal weather conditions; however, no attempt was made to define the mean and the variance around the norm.

2. Economics

a. Underlying Assumptions

The analyses which were performed to determine the economic benefits were subject to data limitations which required several critical assumptions. The following are the major limitations and the resulting assumptions:

(1) Published data or experimental results that would identify possible changes in yield, given the cancellation of pronamide, were unavailable. Therefore, based on the knowledge of weed specialists[1] who are familiar with the practices used for growing lettuce in California and Arizona, the Agency assumed that current levels in yield would be maintained, except in the Salinas and Santa Maria Valleys where 18,400 acres would experience a 20 percent loss in yield due to inclement weather (as discussed in the Biology Section). Although there are no firm data or experimental findings to support the latter effect, the Agency used this assumption to reflect the consequences of its potential policies under differing agronomic situations.

---

[1]

Salinas Valley	H. Agamalian,	U. of California Extension Service
Coastal Region	A. Lange,	U. of California Extension Service
Imperial/Blythe	D. Cudney,	U. of California Extension Service
Arizona	K.C. Hamilton,	U. of Arizona Extension Service

(2) Published data specifying alternative weed-control strategies by each region was unavailable. Therefore, based on the knowledge of weed specialists (op. cit.), the Agency assumed that growers would use a benefin/propham treatment for weed control in combination with additional hand labor and mechanical cultivation on all acreage in the Imperial-Blythe area, in Arizona, and in the region identified as "other California." If this assumption is inaccurate and growers cannot chemically control weeds on a significant portion of this acreage, their labor and production costs could increase substantially.

(3) Because of a general lack of data about lettuce production and about the use of pronamide in the "other California" and Arizona regions the Agency assumed that production techniques in these regions would be similar to those reported for Salinas and Santa Maria for "other California" and Imperial-Blythe for Arizona.

(4) Because of the imprecise data which the Agency used to determine the effects on yields and prices the Agency limited the economic analysis in this position document to direct effects on growers. In most instances, the Agency examines a full range of the potential economic effects of a restrictive pesticide policy. In this instance, evaluations of changes in supply and in price would have suggested substantially more credibility in the underlying data than actually existed. This type of analysis

can be refined if and when more precise data become available. The Agency did not consider the seasonal effects which could modify its economic conclusions, because supporting data were not available.

b. Costs of Weed-Control Strategies

The current strategies of weed control combine the use of pronamide (which is sometimes applied in sequential treatments with benefin), hand labor, and machine cultivations. If the registration for the use of pronamide on lettuce were cancelled, growers could adopt one of three alternative strategies. The chosen strategy would be dependent on location, climatic/environmental factors, and crop rotations.

The costs of weed-control strategies vary by region in response to cultural practices, climatic/environmental conditions, and weed spectrum. If the registration for the use of pronamide were cancelled and new weed-control strategies adopted, the costs of weed control would increase. Table III-4 identifies the additional costs of weed control which would be incurred by growers if the Agency cancelled the registration for the use of pronamide on lettuce. When alternative chemical controls can be used in combination with increased levels of hand and mechanical cultivation, costs of weed control would increase by approximately $45 to $55 per acre representing a 2.4 to 3.0 percent increase in the costs of production ($1,818 average production cost per acre).

Table III-4
Comparison of Minimum Costs Per Acre of Pronamide and Alternative Weed Control Measures[8]

Herbicides	California				Arizona
	Salinas Valley	Santa Maria Valley	Imperial, Blythe	Other California	
	dollars				
Pronamide					
Pronamide Cost[1]	8.50	15.30	18.70	8.50	18.70
Application Cost	6.05	6.05	6.05	6.05	6.05
Total Cost (less base labor value)	14.55	21.35	24.75	14.55	24.75
Benefin-Propham					
Benefin Cost[2]	2.44[6]	5.18	6.11	2.44[6]	5.11
Peopham Costs[3]	11.40	—[7]	11.40	11.40[6]	11.40
Soil incorporation costs	4.60	11.50	11.50	4.60[6]	11.50
Additional hand labor	40.00	40.00	40.00	40.00	40.00
Additional cultivations[4]	10.00	10.00	5.00	10.00	5.00
Total additional costs	68.44	66.68	74.01	68.44	74.01
Differential (less base labor value)	53.89	45.33	49.26	53.89	49.26
Non-Chemical[5]					
Additional Hand labor	150.00	150.00			
Additional cultivations[4]	15.00	15.00			
Total additional costs	165.00	165.00			
Differential (less base labor value)	150.45	143.65			

---

[1] Grower costs for pronamide $17.00 per lb. a.i. (USDA/State Assessment Team, 1977).

[2] Grower costs for benefin $11.10 per gallon, 1.5 lb. a.i. per gallon (USDA/State Assessment Team, 1977).

[3] Grower costs for propham $9.50 per gallon, 2 lb. a.i. per gallon (USDA/State Assessment Team, 1977).

[4] Grower costs of $5.00 per acre for each additional cultivation.

[5] Non-chemical weed control programs would only be used in Salinas and Santa Maria Valleys where weather, soil conditions and rotations preclude the use of benefin.

[6] Sequential treatments of benefin and pronamide are currently used on 30 percent of the acreage. If pronamide is cancelled, benefin will be used on 50 percent of the acreage. These cost figures indicate the average additional costs per acre of benefin application and soil incorporation charges.

[7] The Santa Maria Valley Weed spectrum does not include weeds controlled by propham (Cisney, 1977).

[8] This table reflects only the additional hand labor and cultivation costs necessary to bring weed control by alternate strategies up to the level of pronamide. There is a base labor value which would be identical for all strategies. This base labor value would not change the differentials calculated.

The preferred alternative strategies would combine chemical and non-chemical weed-controls such as a combination of benefin/propham (propham would not be used in the Santa Maria Valley due to the weed spectrum), hand labor, and mechanical cultivation. The use of benefin/propham (or benefin alone) would require an increased number of hand and mechanical cultivations compared to the number of such cultivations require with use of pronamide.

Without pronamide, the only effective weed-control strategy that could be used on about half of the acreage in the Salinas and on seventy percent of the Santa Maria acreage would be exclusively non-chemical. On this acreage, benefin/propham could not be incorporated into the soil due to rain and heavy-textured soil, or would not be applied due to the longer residual life of benefin. Under a strategy of non-chemical weed control, large amounts of hand labor and numerous machine cultivations are required. Although herbicide costs would be eliminated on this acreage, additional hand and mechanical cultivation would increase the costs of weed-control by approximately $145 to $150 per acre, resulting in a 7.9 to 8.2 percent increase in the costs of production.

C. Impacts

If the Agency were to cancel the registration for the use of pronamide on lettuce, the growers would be affected by the increased costs of controlling weeds on all lettuce acreage which they currently treat with pronamide, and by a potential for decreased yields on 25% of the Santa Maria and Salinas Valley acreage. When growers could practice alternative chemical-weed-control strategies and maintain yields, their losses in net revenue would be approximately $50 to $55 per harvested-acre as indicated in Table III-5.

In the Salinas and Santa Maria Valleys, the cancellation of the registration of pronamide could result in the adoption of non-chemical strategies of weed control. In that event, and if yields were maintained, net revenues would be reduced from $567 to $417 and from $567 to $423 per harvested acre, respectively, as indicated in Table III-6. As indicated earlier, however, the cancellation of the registration for pronamide could result in reductions in yield in these areas. These losses in yield could occur because of the combination of rainy weather and heavy textured soils which could prevent growers from cultivating fields at the optimal time, thus forcing seedling lettuce to compete with weeds. Under conditions such as these, the cancellation of the registration for pronamide's use could result in reductions in net revenue for the grower of from $567 to $159 and $567 to $165 per harvested acre in the Salinas Santa Maria Valleys respectively.

Reproduced from
best available copy.

Table III-5

Net Revenue Changes per Acre per Harvest Associated with the Cancellation of Pronamide to California and Arizona Lettuce Growers using Alternative chemical Controls

Region	With Pronamide			Cancellation of Pronamide using alternative chemicals			Net Revenue Losses Using Alternative Chemicals
	Gross[1] Revenue	Production Costs	Net Revenue	Gross Revenue	Production Costs	Net Revenue	
	- - - dollars per acre - - -			- - -dollars per acre - - - - -			dollars per acre - -
California							
Salinas (300 cwt)	2400	1833	567	2400	1887	513	54
Santa Maria (300 cwt)	2400	1833	567	2400	1887	513	54
Imperial/Blythe (234 cwt)	1872	1804	68	1872	1853	19	49
Other	NA[2]	NA	NA	NA	NA		NA
Arizona (238 cwt)	1904	1804	100	1904	1853	51	49

[1] Assumes lettuce price of $8.00 per cwt.
[2] Data unavailable.

Source: Table 17, Preliminary Assessment of Benefits of Pronamide, EPA, 1978

Reproduced from best available copy.

Table III-6
Net Revenue Changes per Acre associated with the cancellation of Pronamide to Salinas and Santa Maria valley Lettuce Growers Using Non-chemical Weed Controls

	With Pronamide			Cancellation of Pronamide using Non-chemical Weed Alternatives			Net Revenue Losses from using Non-chemical control
	Gross Revenue 2/	Production Costs	Net Revenues	Gross Revenue	Production Costs	Net Revenues	
	- - - - - - - - - - - - - - - - - - - -dollars per acre -						
California							
Salinas							
yield 300 cwt	2400	1833	567	2400	1983	417	150
yield 240 cwt 1/	-	-	-	1920	1761	159	408
Santa Maria							
yield 306 cwt	2400	1833	567	2400	1977	423	144
yield 240 cwt 1/	-	-	-	1920	1755	165	402

1/ Custom harvest rates are charged on a piece bases at the rate of $1.85 per carton. A 20 percent yield reduction would reduce the harvesting portion of production costs approximately 20 percent from $1,110 to $888 per acre.

2/ Assumes price of $8.00 per cwt.

Sources: Table 17. Preliminary Assessment of Benefits of Pronamide, EPA, 1977, The estimated annual cost to lettuce growers in California and Arizona, if the Agency were to cancel the registration for pronamide's use, and assuming the yield effect, would be $15.1 million of which approximately $10.34 million would be in additional production costs and $4.3 million in net revenue loss (production losses minus reduced harvest cost). [See Table III-7].

The areas most affected by a possible cancellation of pronamide's registration are the Salinas and Santa Maria Valleys which currently produce 41 percent of U.S. lettuce. It is estimated that the cost of lettuce production could increase by $6.2 million and $1.6 million in Salinas and Santa Maria, respectively. Furthermore, average annual yields could decline by approximately 5 percent, creating a loss in net revenue of $4.8 million in the Salinas and Santa Maria areas (ignoring the subsequent effects of price adjustments in the marketplace).

The costs to the growers in the Salinas Valley who transplant lettuce seedlings directly into the fields were not quantifiable. If pronamide were cancelled, these growers could utilize alternate herbicides or revert to the technique of seeding lettuce directly into the fields. However, there was no data presented to develop the quantitative impacts which could occur. For purposes of this document, total impacts, whether from direct seeding of lettuce or from transplant lettuce, are included together.

Reproduced from best available copy.

Table III-7
Aggregate User Impacts[1]

	California				Arizona	Total
	Salinas Valley	Santa Maria Valley	Imperial Blythe	Other California		
Acreage Using Pronamide	60,400	13,200	26,500	14,550	9,250	123,900
Acreage Using Chemical Alternatives	30,200	3,300	26,500	14,550	9,250	83,800
Additional Costs Per Acre	$53.89	$45.33	$49.26	$53.89	$49.26	$51.58
TOTAL	$1,627,478	$149,589	$1,305,390	$784,100	$455,655	$4,322,212
Acreage Using Non-Chemical Alternatives	30,200	9,900				40,100
Additional Costs Per Acre	$150.45	$143.65				$148.77
TOTAL	$4,543,590	$1,422,135				$5,965,725
Total Additional Costs of Lettuce Production	$6,171,068	$1,571,724	$1,305,390	$784,100	$455,655	$10,287,937
Acres Experiencing Yield Loss Due to Weather Conditions[2]	15,100	3,300				13,400
Gross Revenue Loss Per Acre[3]	$480	$480				$480
Harvest Cost Reduction[4]	$220	$220				$220
Revenue Loss (Gross Revenue loss-Harvest Cost Reduction) Per Acre	$260	$260				$260
Revenue Loss resulting from yield decline	$3,926,000	$858,000				$4,784,000
Total cost of Pronamide Cancellation	$10,097,068	$2,429,724	$1,305,390	$784,100	$455,655	$15,071,937

---

[1] Based on estimated 1977 acreage, 1977 costs, and 1977 prices and assuming an adequate labor supply.

[2] Assumes 25% of the Salinas and Santa Maria Valley will experience a 20% yield decline resulting from delays in timing of cultivations and hand labor due to rainy winter climate (Agamalian, 1977b).

[3] Assumes current yield of 30,000 lbs. per acre and price of $8.00 per hundred weight

[4] Custom harvest rates are charged on a piece basis.

C. Alfalfa

1. Biology of Weed Control

a. Alfalfa Hay

Alfalfa is a perennial legume grown for forage throughout the United States. In 1976, it was reported that 27,000,000 acres of alfalfa hay were grown. 94,500 of these acres, or 0.35%, were treated with pronamide. The problem-weed spectrum encountered by growers and controlled effectively by pronamide is found only in the Northeast, the Midwest, and in the irrigated West. Of the total acres of alfalfa in these areas (9,000,000 acres in the Northeast and upper Midwest and 4,500,000 acres in the irrigated West), pronamide is applied to 67,500 acres and 27,000 acres, respectively. These acreages represent 0.6% of the total alfalfa-acreage on which pronamide is efficacious. However, pronamide is a relatively new tool for weed-control in alfalfa, and growers are still in the process of accepting it (Ryan, 1977; USDA, 1977).

For the irrigated alfalfa grown in the West, the major weed pests are downy brome and other sharp-awned winter annual grasses which reduce hay palatability and seriously injure cattle, and perennial grasses such as quackgrass, bluegrass, and perennial ryegrass which reduce the amount of alfalfa (and therefore the protein amount) harvested per acre of hay mixture and shorten the life of the alfalfa stand (USDA, 1977). On this irrigated land, new stands are commonly planted in August, following the harvest of a rotational crop. In these new plantings, competition from winter annual and perennial weeds are competitors of the seedlings. Such weeds, if not controlled by a herbicide, prevent the successful establishment of alfalfa or reduce the quality of the hay harvested from the first cutting during the following summer (USDA, 1977). Pronamide achieves the most effective control of downy brome and quackgrass.

New plantings in the Midwest and Northeast are commonly made in the spring. Summer weeds threaten stand establishment and must be controlled at the time of planting. Current agricultural practice is to plant a companion small grain crop in the row spacings to shade out the weed seedlings, as well as to provide a cash crop for the first year. After the grain is harvested, the alfalfa extends rapidly into the row spacings, thereby reducing the potential of future weed infestations. The plants from the germinating grain seeds can compete with the alfalfa and therefore sometimes require herbicidal control.

In established stands, during the fall of the second through the fourth or fifth year, pronamide is applied to the dormant alfalfa to control winter weeds and grasses particularly when either quackgrass or downy brome control is needed. Pronamide applied at this time controls weeds to the extent that another growing season can generally be expected from the alfalfa (USDA, 1977).

In new fall plantings of irrigated alfalfa in the West, only two herbicides, pronamide and propham, are safe on alfalfa seedlings. They can be applied after the 3 trifoliolate leaf stage to reduce competition from perennials and fall-germinating winter annuals. Pronamide gives more reliable control than propham, due to the latter's volatility which requires that it be incorporated into the soil by water immediately after application.

In the Midwest and Northeast, the major weed pest in established alfalfa stands is quackgrass. Although quackgrass has some nutritional value, its protein content is significantly lower than that of alfalfa, especially in the first cutting of the season (USDA, 1977; J. Doll, 1977). Winter annual weeds also contribute to lower protein content. Thus, the major benefit from pronamide's use in those areas stems from the control of quackgrass.

The control of weeds in alfalfa acreage increases the per acre protein content of the hay mixture and therefore reduces the cost of satisfying the protein requirements for dairy cattle. Recent economic studies which document the increased cash value of hay mixtures composed mostly of high-protein alfalfa as well as the increased milk production resulting from this alfalfa have probably contributed to increases in the use of pronamide (USDA, 1977).

When planting a field of alfalfa, growers may use soil incorporation of a preplant, preemergent herbicide instead of planting a companion crop to control grassy weeds. In this instance, broad leaf weeds are controlled by 2,4-DB, or dinoseb which growers would apply as a postemergent spray. Pronamide generally cannot be used as a spring treatment in companion cropping situations because of its phytotoxicity for the grain in question.

Alternative herbicides are rated only two-thirds as effective as pronamide for use in established alfalfa stands (USDA, 1977). Also, pronamide is the only herbicide that effectively controls perennial grasses in alfalfa. A vigorous stand of established alfalfa will shade out most summer weeds thereby minimizing herbicide requirements in established stands. Table III-8 summarizes the features of pronamide and its alternates.

b. Alfalfa Grown for Seed

Acreage planted in alfalfa which is grown for seed is a small segment of the total alfalfa acreage. As shown in Table III-I, only 237,000 acreas of all legumes were grown for seed in 1977. Pronamide is used in this segment because it controls both summer and winter weeds. Seed alfalfa is planted in a wider row spacing than hay alfalfa to allow for efficient insect pollination and seed set. This practice eliminates the seed alfalfa's ability to crowd out weeds. Therefore, a high degree of weed-control is necessary to maintain the requirements of purity for the production of commercial seed.

Table III-8
Relative Efficacy of Herbicides Used on Forage

Herbicide	Crops[1] (N = new, E = established)				Soil Types		Weeds Controlled[2]				
	Alf	Clov	Tref	Sain	Loamy	Sandy/Gravelly	Downy Brome	Winter Annuals Grasses	Winter Annuals Broadlf	Perennial Grasses	Dodder
Pronamide	N,E	N,E	N,E	N,E	yes	yes	x	x	(x)[4]	x	x
Propham	N,E	N,E	N,E		yes	yes	x	x			x
Chlorpropham	E	E[3]			yes	yes	x	x			x
Dichlobenil	E	E[3]			yes	no					x
Diuron	E		E		yes	no	(x)[4]	x	x		
Paraquat	E				yes	yes	(x)[5]	(x)[5]	(x)[5]		spot trt
Simazine	E				yes	no	x	x	x		
Terbacil	E				yes	no	x	x	x		

[1] Alf = alfalfa, Clov = Clovers, Tref = birdsfoot trefoil, Sain = sainfoin

[2] Major problem weeds, controlled by pronamide

[3] Ladino clover only

[4] Partial control

[5] Used with a selective herbicide

Reproduced from best available copy.

A weed commonly found in alfalfa grown for seed is dodder. This weed not only weakens the alfalfa through competition but is also parasitic to the alfalfa plant. Dodder also reduces the quality of the product by contaminating the alfalfa seed with dodder seed which is very similar to alfalfa seed. Mechanical separation does not effectively separate these seeds, and the marketability of the contaminated alfalfa seed is drastically reduced (USDA, 1977). Pronamide is important in this instance since it provides the better and more consistent control of dodder, summer grasses, perennial weeds, and winter annual weeds than any of the alternates.

2. Economics

a. Underlying Assumptions

The analysis determining economic benefits was performed with data limitations which required several critical assumptions. The following are the major limitations and the resulting assumptions:

(1) There may be a discrepancy in the estimates of pronamide use on alfalfa hay. The U.S. Department of Agriculture indicated that 94,500 acres were treated with pronamide in 1977. Rohm and Haas reports that only 50,000 acres were treated in 1976[1/]. The benefits derived were based on the use of pronamide on 94,500 acres since this value reports total use while the Rohm and Haas value is based on yearly sales.

[1/] It is unclear whether the difference represents growth in pronamide usage during the year or a real discrepancy between the estimates.

(2) Data specifying alternative weed-control strategies for alfalfa and related small-seeded legumes were unavailable. The Agency therefore assumed that, if the registration for the use of pronamide on alfalfa were cancelled, diuron, propham, simazine, and terbacil (alternates identified in Table III-2) would be used on alfalfa hay and seed crops in the irrigated West. The Agency also assumed that alternative chemical weed control practices would not be used on pronamide-treated alfalfa hay in the Upper Midwest and Northeast because no alternative chemical control for quackgrass currently exists.

(3) The documentation of the efficacy of alternative herbicides was not precise. The estimated range in the efficacy of the alternatives was from 50% to 80% of the control offered by pronamide. The value of 66% (two-thirds) represented the mean (Keitt, 1978), which was also consistent with expert opinion.

(4) The analysis only considered the direct benefits attributable to pronamide. No attempt was made to quantify such secondary effects as the increased level of plowdown nitrogen in a pronamide-treated alfalfa field versus a weed-infested alfalfa field, or the rotational advantages of a weed-free field (decreased herbicide costs and increased yields in the following crop). This limitation underestimates the benefits of pronamide use.

(5) No attempt was made to quantify the benefits associated with any future increased use of pronamide in alfalfa and related small-seed-legumes. If an increased use of pronamide occurs, the benefits associated with the use of pronamide would increase correspondingly.

b. Costs of Weed-Control Strategies

Pronamide is applied to alfalfa grown for hay at a cost of $21 per acre; the cost of applying pronamide on alfalfa grown for seed in the irrigated West averages $25 per acre. If the Agency were to cancel the registration for the use of pronomide on alfalfa, alternative herbicides would be used in the irrigated West.

The alternative chemicals ---- diuron, propham, simazine, and terbacil ---- are less expensive to apply but are also less efficacious than pronamide. The costs of alternative herbicides on alfalfa hay in the irrigated West range from $11 to $13.80 per acre. The costs of treating alfalfa seed crops range from $9 to $13.80 per acre. Alternative herbicides would not be used to replace pronamide in the Midwest and Northeast, since no other chemical controls quackgrass in alfalfa hay. The costs of pronamide and alternative herbicides are reported in Table III-9.

Reproduced from best available copy.

Table III-9
Compartive Acre Treatment Costs of Herbicides Used on Alfalfa1/,

Herbicide	Application Rate2/			Price per Pound3/	Comparative Cost per Acre-Treatment3/		
	Irrigated West		Upper Midwest/Northeast4/		Irrigated West		Upper Midwest/Northeast4/
	Hay	Seed	Hay		Hay	Seed	Hay
	- - - - - - pounds - - - - -			dollars	- - - - dollars - - - -		
Pronamide	1.0	1.0-1.5	1.0	16.00	21.00	25.003/	21.00
Diuron	2.4	2.4	—	3.40	13.16	13.60	—
Propham	4.0	4.0		2.20	13.80	13.80	—
Simazine	1.5	1.0	—	4.00	11.00	9.00	—
Terbacil	0.4-0.6	0.5	—	17.00	13.50	13.50	—

1/ Includes birdsfoot trefoil in the Upper Midwest and Northeastern United States.
2/ Of active ingredient.
3/ Includes $5.00 per acre application cost.
4/ Alternative chemicals are not used in the Upper Midwest/Northeast.
5/ Average over range of application rates.

Source: USDA/State Assessment Team, 1977.

c. Impacts

(1) User

The possible cancellation of pronamide's registration for use on alfalfa would result in an annual loss in net revenue for the producers of alfalfa hay and alfalfa seed who currently use pronamide. Growers of alfalfa hay would experience losses in net revenue of $8.05 and $38.14 per acre in the irrigated West and Midwest and Northeast, respectively. Producers of alfalfa seed who use pronamide would experience losses in net revenue of $36.22 per acre. These changes in net revenue would result from the combination of changes in the costs of weed control, losses in yield, losses in quality (protein in hay and seed free of weed seeds), and decreased longevity of the stand. [See Tables III-9 through III-11].

The total cost to growers could exceed $2.3 million per year for producers of alfalfa hay and seed in the irrigated West and in the Midwest and Northeast (See Table III-12). Hay producers could experience losses in revenue of approximately $1,573,00 to $543,000 in the irrigated West, and $1,030,000 in the Midwest and Northeast. Western seed producers could experience losses in net revenue of approximately $761,000.

Table III-10
Annual Benefits from the Continued Use of Pronamide

Region and Crop	Average Stand Longevity		Cost of Establishment	Average Annual Cost of Establishment over Life of Stand1/		
	Without Pronamide	With Pronamide		Without Pronamide	With Pronamide	Difference
	---years---		---dollars/acre---			
Irrigated West						
Hay	4	5	100	30.19	25.05	5.14
Seed	5	6	150	37.57	32.45	5.12
Upper Midwest/Northwest						
Hay	4	5	100	30.19	25.05	5.14

1/ Establishment costs amortized at 8% interest over varying life spans.

Source: USDA/State Assessment Team on Pronamide, 1977.

Table III-11
Midwest/Northeast Hay Seed - Annual Yield, Quality and Value of Production with the Use of Pronamide and Alternative Chemicals

Treatment	Yield Per Acre		Quality-Related Price Adjustment 1/		Value Per Unit Yield		Gross Revenue	
	Hay	Seed 2/	Hay	Seed	Hay	Seed	Hay	Seed
	tons	pounds	percent		dollars		dollars/acre	
Pronamide	5.0	436	10.0	5.0	71.50	1.05	357.50	457.80
Alternative Herbicides	5.0	402	6.6	3.3	69.29	1.03	346.45	414.06
Difference 3/	0	-34	—	—	-2.21	-0.02	-11.05	-43.74

1/ Alfalfa hay treated with herbicides produces greater protein per ton harvestd than untreated alfalfa. A ton of alfalfa treated with pronamide will contain 10 percent more protein than untreated alfalfa and a ton of alfalfa treated with alternative herbicides will contain 6.6 percent more protein than untreated alfalfa, or 2/3 the increase resulting from the use of pronamide. Alfalfa prices are adjusted for protein content, viz., alfalfa hay treated with brings a 10 percent price premium over untreated alfalfa. Hay harvested from untreated fields has a price of $65.00 per ton. Similar adjustments are made for seed alfalfa, but the price premium results from cleaner seed, i.e. reduced proportions of weed seed per pound of alfalfa seed from treated fields. The adjustments for seed alfalfa are 5 percent for alfalfa treated with the alternative herbicides. Seed harvested from untreated alfalfa fields has a price of $1.00 per pound.

2/ Since most alfalfa grown for seed prduction is treated with herbicides, the 400 lb. average yield per acre estimated by USDA was assumed to be the yield obtained with the use of alternative herbicides.

3/ With respect to pronamide treatment.

Table III-12

Alfalfa Grower Impacts Associated with Cancellation of Pronamide

Crop and Region	Pronamide Treated Area	Net Revenue Loss	
		Per Acre	Total
	acres	dollars	dollars
Alfalfa Hay			
West	67,500	8.05	543,375
Upper Midwest/Northeast	27,000	38.14	1,029,780
Total Hay	94,000	——	1,573,155
Alfalfa Seed			
West	21,000	36.22	760,620
Total Alfalfa	115,500	——	2,333,775

(2) Market and Consumer

If the Agency were to cancel the registration for the use of pronamide on alfalfa, the impact on the market would be minor. Between 1973 and 1976, over 27 million acres of alfalfa hay were harvested. It is estimated that only 94,500 acres of alfalfa hay were treated with pronamide in 1977. The total production from these acres was not increased through the use of pronamide. However, the quality (i.e., protein content per harvested acre) of the 418,500 tons of hay produced from pronamide-treated alfalfa was improved an average of 11.0 percent (average of the protein improvement in the irrigated West and Upper Midwest and Northeast). Even if all of the growers of alfalfa for hay who currently use pronamide were to shift to other crops as a result of the Agency's cancellation of pronamide's registration for use on alfalfa, the total production of alfalfa grown for hay in the U.S. would decrease by less than 1 percent[1/]. This change in the production of alfalfa grown for hay would not be large enough to result in significant impacts on the market.

During 1977, over 93.6 million pounds of alfalfa seed were produced in the United States. The use of pronamide, rather than the available alternative herbicides, on 21,000 aces of alfalfa seed is estimated to

---

[1/] If all of the acreage treated with pronamide had been withdrawn from production in 1977, alfalfa hay production would have declined 418,500 tons. This represents only 0.56% of the 128,874,800 ton average annual production.

have increased the total production of alfalfa seed in the U.S. by 714,000 pounds (0.76 percent). Only 21,000 acres of alfalfa grown for seed are currently treated with pronamide. The resulting losses in production, if the Agency were to cancel the registration for the use of pronamide on alfalfa seed, would be small. The impacts on the market, in the event of such a cancellation, would be minor. Since the Agency estimates that the impacts on the market of alfalfa grown for seed would be minor, it expects that the impacts on consumers from its possible cancellation of pronamide's registration for this use would be insignificant.

D. Other Crops

There was an overall lack of quantifiable economic benefits for any of the minor volume uses. Therefore, these uss are addressed in qualitative terms.

1. Berries

Pronamide is used on blueberries and the cane fruit (boysenberries, raspberries and blackberries). This use is primarily confined to Washington and Oregon where 10,000 acres of berries are planted annually. Pronamide is applied on about 50% of the acreage.

Pronamide is applied to control cool weather perennial grasses including quackgrass and weeds. Application is made in the fall after harvesting. Substitute herbicides offer some control of the weeds controlled by pronamide but are more expensive to use (dichlobenil) and can be phytotoxic to the berry plant (dichlobenil and simazine).

2. Woody Ornamentals

In the United States there are 307,000 acres of commercial nuseries. About 17,000 acres were treated with pronamide (Rohm and Haas) to control cool-season perennial grasses.

There are numerous substitute herbicides available, but none of these control the primary pest quackgrass, and other grassy weeds as well as pronamide. Of the substitutes only dichobenil and simazine are registered for suppression (not control) for quackgrass, and these two herbicides are phytotoxic to the plants at the rates necessary for control. In addition, dichobenil cost 2.5 times more per acre than pronamide.

3. Burmudagrass Turf

Pronamide is used as a selective herbicide in bermudagrass turf to control annual bluegrass. An estimated 16,000 acres in the southern U.S. were treated in 1976.

There are no other currently registered herbicides which selectively control annual bluegrass.

4. Sugarbeet Seed

Sugarbeet is grown for seed in three western states (Oregan, Utah, and Arizona). The acreages grown vary in response to projected demand, but usually 4,000 - 5,000 acres of sugarbeets are grown for seed annually. Pronamide is used on about 90% of this acreage.

Propham is the only registered substitute herbicide. Propham's effectiveness is less than that of pronamide, plus the timing of propham's application is critical, as is the need to incorporate propham into the soil. These shortcomings were discussed in the section on lettuce.

IV. Risk-Benefit Analysis of Alternative Courses of Action

A. Introduction

The foregoing review analyzes and summarizes information on the risks and the benefits of the uses of pronamide. This section evaluates a series of regulatory options. Several particularly significant factors stand out.

1. Salient Risk Factors

The available study in mice which indicates that pronamide is an oncogen in mice provides substantial evidence that pronamide poses the risk of cancer to man. In view of the exposure to humans which results from its use, pronamide poses a cancer risk to man of sufficient magnitude to require the Agency to determine whether these uses offer off-setting social, economic or environmental benefits. The key populations at risk are pesticide applicators and the members of the U.S. population who eat lettuce.

At present the risk to the U.S. population from consuming dairy products from cows fed pronamide-treated-alfalfa is small. However, if the use of pronamide increases significantly, this use may present an incremental addition to the risk of a magnitude great enough to warrant further review.

2. Salient Benefit Factors

Pronamide is primarily used as a herbicide on lettuce including endive and escarole varieties. Most use occurs in Arizona and California, which average 85% of the total U.S. lettuce production. A loss of 15 million dollars would result from cancelling the registration for this use. Alternate chemicals are available but are less effective, more costly to use, and would require additional hand labor to attain the same yield per acre. While it is likely that most of this cost would be assumed by the grower, some cost might be passed through to the consumer. Due to the lack of data, it is impossible to quantify the retail price change that might result from the loss of pronamide.

Pronamide is also used as a herbicide on alfalfa and on small legumes grown for hay and for seed. It is used mainly in the irrigated West and in the Midwest/ Northeast. If the Agency were to cancel the registration for this use, growers would lose 2.3 million dollars.

If the Agency were to cancel the registration for pronamide use in alfalfa, there would be no method for controlling quackgrass. Pronamide, the only herbicide registered for this control, is also thought to increase alfalfa stand life by at least one year. Without chemical control, the grower's only alternative to enduring an infestation of quackgrass is to plow the field under.

B. Five Possible Alternate Courses of Action

Evaluation of the risk and benefit data suggests five principal regulatory options:

1. Continue registration of all uses.
2. Continue registration of all uses; amend the terms and conditions of registration.
3. Continue registration of all uses; amend the terms and Conditions of registration; revise the tolerances on lettuce to lower the dietary exposure.
4. Continue Registration of all uses; amend the terms and conditions of registration; revise the tolerances on lettuce to lower the dietary exposure; require a monitoring report on residues in milk from pronamide use on alfalfa at 5 year intervals coincident with reregitration.
5. Cancel all uses.

Tables IV-1 and IV-2 summarize the risks and benefits of each option. The specific risks and benefits pertaining to each option are described below.

1. Continue Registration of All Uses

Adopting Option 1 would indicate that the Agency concludes that the benefits associated with each use outweigh the respective risks and that therefore, none of the uses of pronamide cause unreasonable adverse effects. This option would return pesticide products which contain pronamide to the registration process. This option would not reduce the risk of cancer associated with the use of pronamide. The potential lifetime risk of cancer from all sources would remain at 3×10^{-6} for oral ingestion, assuming dietary lettuce residues at tolerance levels of 2.0 pm. Applicator risk would remain at 9×10^{-5} for alfalfa use and 7×10^{-3} for lettuce use. This option would not result in any adverse economic impacts and would retain the usefulness of pronamide as an economical, effective tool for the control of weeds in lettuce and alfalfa. The choice of this option would indicate that the Agency is willing to tolerate a level of risk greater than the levels of risk estimated in the other options in return for the highest possible benefits.

2. Continue the Registration of Pronamide for All Uses and Amend the Terms and Conditions of Registration

The adoption of option 2 would indicate that the Agency concludes that the benefits of pronamide's continued use outweigh the risks from oral ingestion. However, without a diminution in the exposure to applicators (Tables II-2 and II-3), and considering the projected incidence of tumors which result from it (Table II-5), the benefits derived from pronamide do not outweigh the risks to this applicator population.

a. Discussion of Proposed Restrictions to Reduce Applicator Exposure

(i) Classify Pronamide as a Restricted-Use-Pesticide and Require Applicator Certification

This option is designed to move the use of pronamide out of the open market and to restrict its use to certified applicators.[1] Since pronamide is marketed almost entirely for use by professional applicators (lettuce, turf) and private applicators (alfalfa, commercial nursery), restricting its use by homeowners should not affect the pesticide industry's profits. In theory, requiring applicators to be certified to use pronamide will reduce the hazard from its use because unskilled applicators will not be allowed to use it.

---

[1] The pesticide applicator certification process grants certificates for two types of applicators: professional and private.

(ii) Require the Use of Protective Clothing during the Mixing and the Application of Pronamide

Data from Table II-3 shows the theoretical exposure range that applicators receive during mixing and applying pronamide. Table II-5 indicates the risk levels and the expected cancers associated with the application of pronamide to lettuce and to alfalfa. Under the assumption used in projecting exposure values, 85% of the body is normally clothed. Excluded from normal clothing are the hands forearms neck face, upper chest, and hair. Requiring the use of a protective overgarment and gloves will leave only 3.5% of the body exposed. Thus an additional 80% of the body, normally uncovered would be protected by a one-piece protective overgarment hat, and gloves. A corresponding reduction in risk could be contemplated from this reduction in exposure (Day. 1978).

The risk levels calculated from experiments using pronamide (Kreminski, 1978) and similar pesticides (Jegier. 1964 Wolfe. 1967· Wolfe. 1975) provide a range of values roughly two orders of magnitude apart in applications on both lettuce and alfalfa (Table II-5). The Agency feels that the average level of risk is more closely represented by Jegier. Even the assumption of this median level, 3×10^{-3} (lettuce applicators) reflects a high estimate of risk.

The economic impact of this regulation would be slight. Most applicators commonly wear protective garments.

(iii) Require the Formulation of Pronamide (Wettable Powder) in Water Soluble Bags[1]

Although there is always a minimum level of exposure, the projected range in levels of risk for lettuce and custom applicators and alfalfa growers (Table II-5) is greatly influenced by the degree of care exercised in mixing the pesticide solutions. The adoption of this option would reduce the total exposure from mixing by at least 95% (Day 1978). Water soluble bags containing pronamide would be added to the water; when the bag dissolves, the formulation would then be released and mixed as it is currently done. There would be no dust generated from pouring or from mixing the product. Although the exposure received during application would not be reduced by the adoption of this option, as shown in Tables II-2 and II-3, the exposure related to application is in the order of 3 orders of magnitude less than the exposure received during mixing. Thus, risks related to application would be about the same as oral risks if this option were adopted.

Adopting this option may cause a slight increase in costs. Rohm and Haas has predicted an increase of roughly $0.25 per lb of formulation, if packaged as water soluble bags (Krzeminski 1978). The total increase in the cost of the application of Kerb 50 W would be $0.50 to $0.65 per acre for alfalfa and $0.20 to $0.55 per acre for lettuce. These costs should not significantly alter the economic benefits of pronamide

---

[1] This restriction would apply only to the wettable powder formulation. Granular formulations do not present the dust problems (Day 1978; Jasper, 1978).

The option is useful because it is a passive protective measure. Applicators would not need to take more stringent protective measures than they already do. Also, there would be no need for additional enforcement activities to monitor compliance with the requirement.

(iv) Cancel Hand Spray Use

This restriction would eliminate exposure to applicators from hand sprays. The values in Table II-3 represent the exposure which applicators receive from sitting on a tractor pulling a sprayer It is reasonable to assume that some of the factors which generated these values would also apply when the applicator is standing holding a hand spray, except that the applicator is within 1 foot of the spray instead of the several feet away from it on a tractor pulling a sprayer. This would increase the exposure by several orders of magnitude. Thus, an applicator using spot-treatment for alfalfa or for any of the other uses may receive from 0.1 mg/kg to 1.0 mg/kg dermal exposure and a corresponding increase in inhalation exposure.

The cancellation of the registration for this use would have a negligible impact on the economics of pronamide. Pronamide is used in hand sprays infrequently, if at all, in spot-treating alfalfa fields, and it is not used at all in lettuce fields. Cancellation would cause the grower to use tractor spray equipment for all pronamide applications. No significant difference in exposure is expected when comparing large agricultural tractors to smaller nursery-size tractors which might be prevalent in applying pronamide for other uses than on lettuce and alfalfa (Day, 1978). Also if packaging were to be limited to water soluble bags, it would become illegal for an applicator to tear open the bag in order to mix a limited amount of spray.

3. Continue Registration of All Uses; Amend the Terms and Conditions of Registration; Revise the Tolerances on Lettuce to Lower the Dietary Exposure

Adopting Option 3 would indicate that the Agency concludes that the risks associated with the ingestion of residues of pronamide, as the pesticide is presently registered, outweigh the benefits of its continued use, but that by revising the tolerance for lettuce which is established by EPA under the Federal Food Drug and Cosmetic Act (FFDCA), the exposure and the consequent risk of tumor production will be reduced to a level at which the benefits from the use of pronamide would outweigh the risks of ingesting its residues.

There are five food sources through which people may ingest residues of pronamide (Table II-1). The cumulative total of four of these (berries, eggs, meat, and milk and other dairy products) is 0.0001 mg/person/day (Day and Collier, 1978). Residues from the fifth food source, lettuce, may vary from 0.0008 to 0.01 mg/person/day depending on the rate at which the pronamide is applied, the method of application, environmental factors and most significantly, the preharvest interval.

Based upon a 35-day preharvest interval, and a 2 ppm tolerance in lettuce, the hypothetical lifetime incidence of cancer in the U.S. population from the ingestion of residues of pronamide from all food sources is 3 cancers per million people. However, by assuming other than tolerance levels in lettuce, the incidence of cancers due to pronamide can be decreased (Table II-5).

There are reasons for assuming that the actual residues of pronamide in lettuce correlate with the residue levels calculated from a 14C-pronamide time decline curve. These reasons include both market basket analyses (Rerig, 1977) and monitoring studies (Alford, 1978) which demonstrate that head lettuce with a preharvest interval of at least 60 days will have measured residues of < 0.1 ppm. Accordingly, since pronamide is normally applied as a pre-emergent at the time of planting, there is, when normal agricultural practices are used, a preharvest interval greater than the minimum of 35 days.

The Residue Chemistry Branch, EPA, upon reevaluating the Rohm and Haas data, has suggested a revision in the lettuce tolerance. This revision would lower the tolerance to 1 ppm with a requirement that the lettuce be treated with pronamide as a pre-emergent and that the minimum preharvest interval be 60 days (Cummmings 1978). This tolerance will force all residues of pronamide to be less than 1 ppm and will lower the exposure to people. The reduced exposure will decrease the projected tumor incidence to a range of from 1 tumor per million people to 1 tumor per 10 million people (Albert, 1978).

Spring and summer leaf lettuce which makes up 5% or less of the total lettuce grown in the U.S., can have a growing season of less than 60 days. If the Agency were to adopt this option, the growers of this type of lettuce would be forced to use a substitute herbicide to control weeds. However, since substitutes are readily available and reasonably economical to use, the impact of the Agency's adoption of this option on the growers of this type of lettuce would not be significant.

4. Continue Registration of all uses, Amend the terms and conditions of Registration, Revise the tolerances on lettuce to lower the dietary exposure; Require a monitoring report on residues in milk from pronamide use on alfalfa at 5 year intervals coincident with reregistration

The data available to the Agency indicates that the present use of pronamide on alfalfa presents a minimal hazard, due to the extremely small percentage of the total crop being treated with the herbicide. However, the Agency does not feel that this relatively safe level can be maintained if the use of pronamide becomes as widespread as predicted by Rohm and Haas (Rarig, 1977). The exposure to the United States population will increase as pronamide is integrated into alfalfa treatments in a wider area of the country. Recently conducted milk and alfalfa hay studies (Kutz, 1978) have shown low residues of pronamide in alfalfa (approximately 0.1 ppm) and possible residues in milk (less than 10 ppb). The increased use of pronamide could result in higher residues, and in higher dietary exposure for a larger segment of the population. Accordingly, the Agency plans to require, at 5-year intervals coinciding with reregistration, surveys for residues of pronamide in milk from dairy cattle fed alfalfa treated with pronamide in the areas where pronamide is marketed.

The economic impact of this option would be an expenditure by the registrant estimated at less than $10,000 every five years.

5. Cancel All Uses

Adopting Option 5 would indicate that the Agency concludes that the risks associated with all of the uses outweigh the respective benefits and thereby result in unreasonable adverse effects. This option would eliminate all of the uses of pronamide. Cancellation would eliminate all of the cancer risk associated with the use of pronamide (Tables II-4 and II-5), but at a cost to growers of 15 million dollars per year for lettuce and 2.3 million dollars per year for alfalfa (Tables III-7 and II-13). Some percentages of the added cost of production might be passed on to the consumer, particularly in the case of lettuce. However, price information and elasticity are not adequate to predict the incremental cost additions to retail prices that would result from the additional costs to the growers (Zygadlo, 1978)[1]. The choice of this option would indicate that the Agency is unwilling to tolerate the level of risk associated with any use of pronamide.

This option would increase the use of alternate chemicals. In lettuce, the two major alternatives would be propham and benefin, used either singularly or in combination. In alfalfa, if the pest weed is not quackgrass for which no other herbicide is presently registered, propham would again be used along with diuron, chloropropham, simazine, and terbacil.

---

[1] In addition to the cost increases for the major uses in alfalfa and lettuce, there would likely be some additional, although unquantified, cost increase for the products of "minor" uses of pronamide.

Propham is currently under RPAR review as a suspected oncogen. Studies used in this review have not been reviewed by the propham RPAR support team so no conclusions on the validity of the studies nor on the oncogenic potential of the chemical can be made now.[1] Propham may also be a teratogenic agent. A study on file indicates that a teratogenic response was achieved in mice. Again, the study has not been reviewed by the propham RPAR support team, so no conclusions can be drawn (Gardner, 1978). Finally, certain toxicological studies have been conducted on propham by Industrial Bio-Test Laboratory. These tests include many of the registration requirements for acute and subacute toxicity. Accordingly, until the registrant of propham can validate these studies, they cannot be used to evaluate the toxicological profile of propham (Gardener and Sandusky, 1978).

Benefin, the other primary alternate to pronamide for use in lettuce is not currently under RPAR review. However, a profile of the toxicological characteristics of benefin indicates that there is a potential for adverse reproductive effects. Although not well documented, there are also indications that benefin may cause mutagenicity, oncogenicity, and neurotoxicity.

Chloropropham is a third alternative to pronamide for use in alfalfa There are data gaps chloropropham regarding its potential for teratogenic, mutagenic, and reproductive effects; chloropropham has also been reported to be oncogenic if it is used along with a promoting agent (Gardener and Sandusky, 1978).

C. Comparison of Options

In selecting a regulatory option, the Agency must decide which of the proposed options achieves the most appropriate balance between risks and benefits. This decision turns in part on the key factual elements summarized above, and in part on the relative merits of each proposed option.

Option 1, which would continue the registration for all uses and Option 5, which would cancel the registration for all uses, represent all or nothing approaches to regulating. With the adoption of Option 1, the Agency would neither do anything to reduce the estimated risks, nor would it otherwise recognize that the RPAR review confirmed the presumption of oncogenicity. By contrast, Option 5 would succeed in eliminating risk, but only by substantially increasing the costs for the users who would be forced to use alternate pesticides. Also, the adoption of this option would eliminate a pesticide which may prove to pose less of a risk than the alternatives.

Options 1 and 5 are even less supportable in light of the range of measures described in Options 2 through 4, which reduce risk without a significant impact on benefits and avoid the costs associated with a cancellation. Option 1 would be reasonable only if the benefits clearly outweigh the risks, and if reductions in risk cannot be achieved without unacceptable consequences for the benefits. Option 5 would be reasonable only if the risks clearly outweigh the benefits, and if significant reductions in risks cannot be achieved by measures short of cancellation, without unacceptable impacts on the benefits. The facts indicate that neither situation prevails and that alternative options are available which are environmentally and economically sound. Therefore Options 1 and 5 are not reasonable regulatory measures in this case.

Option 2 deals with the issue of risk to the applicator through exposure by reducing this exposure and risk with amendments to the terms and conditions of registration. This option, however, does not lessen certain dietary risks that are created through the use of pronamide in lettuce and alfalfa.

Option 3 presents a control for lessening the risk from the use of this herbicide on lettuce and Option 4 combines the previously mentioned controls with an added

Reproduced from best available copy.

Table IV-1
Regulatory Options and Maximum Cancer Risk Incidence Predicted from Pronamide Use

Option	Alfalfa Applicators	Lettuce Applicators	Consumer
1. Continue Registration All Uses	8.93×10^{-5}	6.73×10^{-3}	3.01×10^{-6}
2. Continue Registration All Uses, Amend the Terms and Condition of Registration			3.01×10^{-6}
i. Protective Clothing	8.93×10^{-6}	6.73×10^{-4}	
ii. Water Soluble Packaging	8.28×10^{-7}	8.28×10^{-7}	
iii. Certified Applicators/ iv Restricted Use	No DATA Reduced Exposure Expected	NO DATA Reduced Exposure Expected	
3. Continue Registration All Uses, Amend the Terms and Conditions of Registration, Revise the Tolerance on Lettuce to Lower the Dietary Exposure	Same as Option 2 plus		1.21×10^{-6} to 1.01×10^{-7}
4. Continue Registration All Uses, Amend the Terms and Conditions of Registration, Revise the Tolerance on Lettuce to Lower the Dietary Exposure, Require a Monitoring Report on Residues in Milk from Pronamide Use on Alfalfa at 5 Year Intervals Coincident With Registration	Same as Option 3 plus Monitoring for Potential Dietary Increase resulting from increased pronamide use.		
6. Cancel All Uses	0	0	0

Reproduced from best available copy.

Table IV-2
Pronamide Regulatory Options and Economic Impacts

Option	Commodity	Economic Impact
1. Reregister All Uses	Lettuce Alfalfa	None None
2. Continue Registration All Uses, Amend the Terms and Conditions of Registration		
i. Protective Clothing	Lettuce Alfalfa	No significant impact No significant impact
ii. Water Soluable Packaging	Lettuce	Application Cost increase $.55/acre - No long term economic impact. Net profit loss will be insignificant.
	Alfalfa	Application Cost Increase $.65/acre No long term economic impact. Net profit loss will be insignificant.
iii. Certified Applicators/ Restricted Use	Lettuce Alfalfa	No significant impact No significant impact
	Lettuce	No effect - not use in lettuce beds
iv. Cancel Hand Sprays	Alfalfa	No significant effect
3. Continue Registration All Uses, Amend the Terms and Conditions of Registration, Revise the Tolerance on Lettuce to Lower Dietary Exposure	Lettuce	(Same impacts as Option 2 plus) No impact on the majority of the short season leaf lettuce and all of the head lettuce. Only 10% or less of the total lettuce acreage will require an alternate herbicide. No decrease in production likely.
4. Continue Registration All Uses, Amend the Terms and Condiditions of Registration, Revise the Tolerance on Lettuce to Lower Dietary Exposure, Require a Monitoiring Report on Residues in Milk from Pronamide Use on Alfalfa at 5 Year Intervals Coincident with Reregistration	Alfalfa	(Same impacts as option 3 plus) No significant impact. The analysis costs $10,00 or less every five years.
5. Cancel All Uses	Lettuce	Users - A net revenue reduction $10 - $15 million dollars is projected
	Alfalfa	Users - A net revenue reduction $2.3 million is projected

precaution necessitated by the potential for dietary exposure from the use of the herbicide on alfalfa that is fed to dairy cattle.

V. Recommended Regulatory Action

The Agency recommends Option 4 as its regulatory action:

> Continue Registration of all uses, Amend the terms and conditions of registration (*Note), Revise the tolerances on lettuce to lower the Dietary Exposure, Require a monitoring report on residues in milk from pronamide use on alfalfa at 5 year intervals coincident with reregistration

The analysis of risks and benefits from the continued use of pronamide in both lettuce and alfalfa indicates that the primary problem is the exposure incurred by applicators of the pesticide. The analysis also indicates that a risk from the continued use of pronamide exists for the general population of the United States from eating lettuce which bears residues of pronamide. The amount of this risk for the general population is much lower than the amount of risk which exists for applicators of pronamide. Option 4 represents a responsible regulatory assessments of the risks and the benefits of the continued use of pronamide and the balance between them that should be properly struck.

---

*(i) Classify Pronamide as a restricted use pesticide and require applicator certification.
(ii) Require the use of protective clothing during mixing and application of Pronamide.
(iii) Require the formulation of pronamide (Wettable Powder) in water soluble bags.
(iv) Cancel hand spray use.

Option 4 has distinct components, each of which is designed to reduce the risks of cancer which are associated with the exposure to pronamide without simultaneously creating the adverse economic, social and environmental impacts associated with cancellation. The first requires applicators to become aware of the hazards involved and denies the use of the pesticide to untrained, non-skilled applicators. This requirement would apply to all pronamide products. This option also requires the use of protective overgarments thereby allowing for the safe use of the pesticide during the processes of mixing and applying it which are the periods of potential high exposure. The option would also require the packaging of pronamide as a wettable powder in water soluble bags. This would lessen the exposure which results from opening the bag containing the pesticide, and from mixing it. In practice, the adoption of Option 4 would eliminate applying pronamide with a hand spray because of the requirement that the pesticide be produced in bags of one pound or more in size. Eand spraying, as practiced, is for spot treatment using a total capacity of 1 gallon or less. Spot treatment requires quantities of pronamide in ounces, a feasible mixing capacity for a hand spray. Restricting the formulation to one pound or larger water soluble bags, which are to be used intact, essentially eliminates the hand spray problem in theory. The option's specific cancellation of hand spraying eliminates the problem in fact.

The analysis of cancer risk from the ingestion of treated lettuce presents a small numerical risk, if it is assumed that dietary residues are in the lower part of the residue spectrum exemplified in Table II-2. However, because sufficient data is not available to support this assumption, it is incumbent upon the Agency to act on the side of safety. Consequently the Agency must act to insure a lowering of the actual amount of residues consumed by people. To do this the Agency proposes to require modifications of the label as follows:

1. Applications of pronamide are restricted to pre-emergence only;
2. The application rate cannot exceed 2 pounds active ingredient per acre;
3. Pronamide is not to be applied to lettuce varieties which will be harvested sooner than 60 days from treatment.

This should lower the residues in lettuce to between the 0.8 ppm level and the sensitivity level of 0.01 ppm. As a result the ultimate risk of cancer from the ingestion of lettuce treated with pronamide should be reduced to under one per million population, possibly approaching one per ten million population. At this level, the Agency feels that the benefits will outweigh the risks and that the continued use of pronamide can be supported.

Since an equilibrium between benefits and risks appears to be reached for alfalfa except for the risk to applicators, the Agency does not now feel compelled to exercise any further restrictions on this use. However. the Agency is concerned that a hazard may develop from the residues of pronamide in milk, if pronamide's market share grows to levels predicted by the registrant. The literature which is available indicates that pronamide has not been detected in milk at a sensitivity of 0.01 ppm (Kutz, 1978; Rarig, 1977). However, in an Agency study using sophisticated gas chromatography/mass spectrometry, some low residues of pronamide (<10 ppb) may have been detected in milk. These results have not been confirmed. Therefore, the Agency will require a market basket monitoring study of residues of pronamide in alfalfa and milk to be submitted with every reregistration application for pronamide. If this monitoring shows that concentrations of pronamide are increasing, the Agency will reevaluate the decision on alfalfa.

This option does not impose any severe economic limitations on the use of the pronamide. The primary economic impacts of this option will be in the cost of water soluble packaging and in the elimination of the use of pronamide on lettuce grown in less than 60 days. As discussed in Section IV, the additional cost per pound of active ingredient in water soluble packaging is estimated to be $0.50 (Krzemenski 1978). Computing this on a per acre cost equals an additional cost of roughly $0.50 per acre for lettuce and alfalfa. This additional cost is negligible when compared to the net benefits of pronamide which are, at a minimum, $70 per acre. The remainder of the costs necessitated by this action are also negligible. These costs, as pointed out in Section IV, accrue mainly to applicators and do not cause them to purchase sophisticated equipment, but only to use clothing and equipment now available.

The alternatives which would be used for the portion of lettuce production to be excluded from treatment with pronamide would probably not provide any worse hazard to the public. Propham, although its hazards are not totally documented toxicologically, should not, in the small segment of lettuce affected, prove more hazardous to the applicator or to the consumer. Benefin, also should not prove to be more of a toxicological hazard than pronamide. Taken singularly, these alternatives. propham and benefin, would not be as effective on lettuce as pronamide would be. To provide a spectrum of weed control which is comparable to pronamide, these two chemicals must be tank mixed. This diminished capacity for weed control by the grower should only exist until data is provided to assure the Agency that residues found in short season lettuce and in transplant lettuce do not exceed the one ppm tolerance. Because of the relatively small proportion of the lettuce crop involved, the long term consequences of this action should not result in any large disruption in the economic of lettuce production.

In conclusion, the adoption of the recommended regulatory action would serve to minimize the potential for risk, and would also enable the benefits to remain near their current levels.

BIBLIOGRAPHY

Albert, Roy E., M.D., Chairman, Carcinogen Assessment Group (CAG), EPA, October 19, 1978. The CAG's Risk Assessment on Pronamide.

Albert, Roy E., M.D., Chairman, CAG, EPA, April 7, 1978. Memorandum to Richard Troast, Special Pesticide Review Division (SPRD), EPA.

Albert, Roy E., M.D., Chairman, CAG, EPA, July 28, 1978. Registration of Tumor Initiating Compounds. Memorandum to Edwin L. Johnson, Deputy Assistant Administrator (DAA), Office of Pesticide Programs (OPP), EPA.

Albert, Roy E., M.D., Chairman, CAG, EPA, March 17, 1977. Preliminary Review of Oncogenicity of Pronamide.

Alford, Harold G., Regional Coordinator, Pesticide Impact Assessment Program, Cooperative Extension, University of California, Berkeley, June 6, 1978. Letter to Richard Troast, SPRD, EPA with attachments.

Clark, G.N., O.M. Scott and Sons, June 2, 1977. Request for 60 Day Extension #2 [30000/14] OPP, EPA.

Coberly, R., Toxicology Branch, Registration Division, OPP, EPA, November 29, 1974. 3,5-dichloro-N-(1-1-dimethyl-2-propynyl) benzamide (Kerb), Memorandum to Jesse E. Mayes, Acting Chief, Coordination Branch, Registration Division, EPA.

Cummings, J.G., November 7, 1978. Pronamide RPAR - Regulatory Options. Memorandum to Richard Troast, SPRD, EPA.

Day, H.R., September 5, 1978. Pronamide Exposure - Small Tractors. Memorandum to Richard Troast, SPRD, EPA.

Day, H.R., September 28, 1978. Applicator Exposure Reduction Protective Clothing. Memorandum to Richard Troast, SPRD, EPA.

Day, H., and C.W. Collier, EPA, July 6, 1978. Pronamide Exposure Analysis.

Day, H.R., November 13, 1978. Rohm and Haas Comments on Pronamide Analysis. Memorandum to R. Troast, SPRD.

Dubin, I.M., March 17, 1978. Consultant Pathology Report on Rohm and Haas Compound "Pronamide (Kerb)" Used in Feeding Experiments in Mice and Rats." Submitted to the EPA Carcinogen Assessment Group.

Kutz, F.W., Ph.D., September 29, 1978. Environmental Monitoring Study for Pronamide. Memorandum to Richard Troast, SPRD, EPA.

Potrepka, Robert F., MEB, CED, EPA, February 17, 1977. Validation of Pronamide (Kerb) Chronic Feeding Studies. Memorandum to Richard Troast, SPRD, EPA.

Rarig, F.J., Vice-President, Rohm and Haas Co., August 29, 1977. RPAR Rebuttal of Pronamide (OPP-30000/14).

Rohm and Haas Co., September, 1974. Application for Permanent Tolerance for Kerb: Alfalfa. Confidential. EPA Pesticide Petition 5F1552.

Rohm and Haas Co., April, 1971. Application for Permanent Tolerance for Kerb: Lettuce. Confidential. EPA Pesticide Petition 1F1139.

Ryan, James B., Research Manager, Agricultural Chemicals - North America, Rohm and Haas Co., December 5, 1977. Kerb Benefits Document for the Rebuttal of the Presumption Against Registration of Pronamide (Kerb). EPA Dockett No. 1 OPP-30000/14.

Swisher, E.M., Rohm and Haas Co., May 19, 1977. Request for 60 Day Extension, #1[30000/14] OPP, EPA.

Troast, Richard, SPRD, EPA, January 14, 1977. Biological Activity of KERB, Export Uses Kerb. Record of Communication with Dr. Ely Swisher, Rohm and Haas Co.

USDA/State Assessment Team on Pronamide, August 29, 1977. Pesticide Impact Assessment Pronamide (Kerb). Coordinated by the Office of Environmental Quality Activities, USDA.